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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,620	05/01/2006	Hyun-Soo Kim	Q94674	3640

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,620	KIM ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response dated September 29, 2008, to the non-final action dated April 29, 2008, has been entered. No claims were cancelled, amended, or newly added.

Claims 1-4 and 6 are pending in the application and are under current examination.

Information Disclosure Statement

The information disclosure statement filed 9/29/2008 is compliant with 37 CFR 1.98(a)(2). Accordingly, the information contained therein has been considered and indicated as such on form.PTOSB/08a

Response & Maintained Claim Rejections - 35 USC § 103

Claims 1-4 and 6 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Furcht et al. (U.S. Patent No.: 7,015,037; effective filing date: Aug. 5, 1999), in view of Kokuzawa et al. (U.S. Patent Application Publication No.: 2006/0134078; effective filing date: Dec. 2, 2002). The rejection set forth on pp. 2-4 of the previous office action dated April 29, 2008 is maintained for reasons of record.

The claims embrace a method of differentiating and proliferating a mesenchymal stem cell into a neural cell comprising the steps of: (1) confluent culturing the mesenchymal stem cell as a pretreatment, and (2) culturing a mesenchymal stem cell in a medium comprising an epithermal growth factor (EGF) and a hepatocyte growth factor (HGF).

The previous office action indicated that Furcht et al. describe the isolation of a sub-population of mesenchymal stem cells from bone marrow mononuclear cells and culturing in media supplemented with various growth factors (the cells are referred to as multipotent adult stem cells; MASC; column 7, lines 1-7; column 14, lines 57-60; column 44, Example 1). The bone marrow mesenchymal cells are further described as able to differentiate into various cells

types, including glial and neuronal cells following culture and induction with various factors that included 0.5-100 ng/ml EGF (column 49, Example 5). Furcht et al. separately describe differentiation media comprising both EGF (0.5-100 ng/ml) and HGF (0.5-1000 ng/ml) for the differentiation of epithelial and endodermal cells (column, 52, Example 7, lines 47-50). Kokuzawa et al., describe a medium containing HGF and EGF inducing neurosphere formation from neural stem cells (Abstract).

Applicants disagree, arguing that Furcht fails to teach confluent MASCs culture prior to the neural differentiation. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that Furcht et al. describe a number of culture conditions where the MASCs are cultured to confluence prior to differentiation with the growth factors. For example, "Differentiation to any muscle phenotype required that MASCs be allowed to become confluent prior to induction of differentiation" (column 21, lines 10-12; limitation of claim 1, step 1); where a sole cytokine was added to confluent MASC maintained in serum free MASC medium for 14 days (column 47, lines 9-10; limitation of claim 4).

Applicants argue that Furcht teaches differentiation of mesenchymal stem cells into bone or muscle cells, not differentiation into neural cells. Such is not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the teachings of Kokuzawa et al. have apparently been dismissed by Applicants. There is no requirement for Furcht et al. to teach each and every limitation of the claims in an obviousness rejection based on a combination of references. As previously indicated, while Furcht et al. do not describe using the combination of EGF and HGF to differentiate the mesenchymal stem cells into neural cells, such combination for neuronal differentiation was known in the prior art of Kokuzawa et al., in describing a medium containing HGF and EGF inducing neurosphere formation from neural stem cells (Abstract; limitation of claim 1, step 2). With regard to the limitation of claim 4, wherein the mesenchymal stem cell is cultured for about 2 weeks in the differentiation medium comprising EGF and HGF, and then HGF is removed, Kokuzawa et al. describe culture comparisons

between differentiation media in the presence of EGF, with or without HGF (Fig. 3b and ¶ [0031], p. 3). It is again noted that such alterations in the composition of differentiation media and culture time were considered routine experimentation in the prior art of cell culture.

In response to Applicants' argument that the references do not expressly or inherently teach confluent culturing as a pretreatment, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Here, Furcht et al. actually teach confluent culturing as a pre-treatment to mesenchymal cell differentiation, and the deficiency for neural differentiation under the instantly claimed conditions is cured by Kokuzawa et al.

Applicants argue that Furcht teaches away from the presently claimed confluent culture of mesenchymal stem cells, as a pretreatment, for neural differentiation. Specifically, with regard to the MASC culture for neural differentiation, Furcht's specification states, "[c]ulture at high density ... was also associated with loss of expansion capacity, and cells did not proliferate beyond 25-30 cell doublings" (column 46, lines 9-12), and "[c]ell densities were maintained between 2-8 x 103 cells/cm2," instead of reaching the confluency (column 45, lines 41-42; & column 49, lines 41-42).

In response, it should be noted that Applicants' arguments are misplaced and entirely out of context. Applicants have cited Example 1 of Furcht et al. (columns 45 and 46) as the basis of their argument. However, Example 1 describes the isolation and establishment of MASCs from bone marrow mononuclear cells, prior to application of conditions for differentiation. The establishment and expansion of MASCs referred to in Example 5, column 49 is a pre-requisite for all subsequent differentiation methodologies described, including the expressly taught confluent culture, referred to above. Thus, there is no teaching away from confluent culture prior to cell differentiation.

Applicants' argument that Kokuzawa fails to teach differentiation of MASCs into a neural cells is not found persuasive, because aside from Applicants' argument against the references individually, the ability of MASCs to differentiate into neural cells was established by

Furcht et al., therefore such limitation has already been expressly taught by one of the references. Both Furcht et al. and Kokuzawa et al. describe the differentiation of stem cells into neuronal cells, and both utilized media comprising EGF and HGF for stem cell differentiation. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings, to use a neuronal differentiation medium comprising the combination of EGF and HGF, as described by Kokuzawa et al., to differentiate the mesenchymal stem cells of Furcht et al., with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to substitute a differentiation medium containing both EGF and HGF for one containing EGF and various other growth factor, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. Applicants should note that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S.-, 82USPQ2d 1385 (2007).

Thus, the rejection is maintained for reasons of record, and the foregoing commentary.

Conclusion

Claims 1-4 and 6 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633